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P01/7700 0.00-0327195.4

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1. Your reference — MG/PMS/PB60595P

2. Patent application number
(The Patent Office will fill in his part) — 0327195.4 — 21 NOV 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

SmithKline Beecham Corporation
One Franklin Plaza, P.O. Box 7929, Philadelphia,
Pennsylvania 19101, United States of America

Patents ADP number *(if you know it)* 5949417004

If the applicant is a corporate body, give the country/state of its incorporation — United States of America

4. Title of the invention — Novel Use

5. Name of your agent *(if you have one)*

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GlaxoSmithKline
Corporate Intellectual Property (CN9 25.1)
980 Great West Road
BRENTFORD
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Patents ADP number *(if you know it)* 8072555006.

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
c) any named applicant is a corporate body
See note (d)

Patents Form 1/77

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Continuation sheets of this form	0
Description	8
Claim(s)	1
Abstract	1
Drawings	0

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Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

Request for preliminary examination and search *(Patents Form 9/77)*

Request for substantive examination *(Patents Form 10/77)*

Any other documents *(please specify)*

11. We request the grant of a patent on the basis of this application

Signature M Gibson Date 21-Nov-03

12. Name and daytime telephone number of person to contact in the United Kingdom

M Gibson 01279 644841

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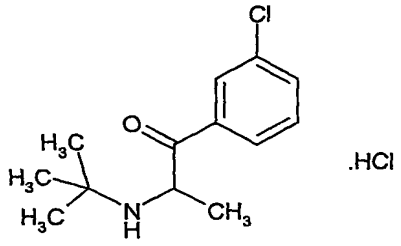
NOVEL USE

This invention relates to a novel use of (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol, in particular its use in the treatment of Restless Legs Syndrome.

Background of the Invention

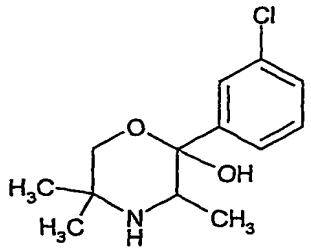
Bupropion hydrochloride, (±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)-amino]-1-propanone hydrochloride, is the active ingredient of Wellbutrin® which is marketed in the United States for the treatment of depression. It is also the active ingredient of Zyban® which is marketed in the United States as an aid to smoking cessation. Bupropion is a relatively weak inhibitor of the neuronal uptake of noradrenaline (NA), serotonin and dopamine (DA), and does not inhibit monoamine oxidase. While the mechanism of action of bupropion, as with other antidepressants, is unknown, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms. Available evidence suggests that Wellbutrin® is a selective inhibitor of noradrenaline (NA) at doses that are predictive of antidepressant activity in animal models. *See* Ascher, J.A., *et al.*, Bupropion: A Review of its Mechanism of Antidepressant Activity. *Journal of Clinical Psychiatry*, 56: p. 395-401,1995.



Bupropion HCl

Bupropion is extensively metabolized in man as well as laboratory animals. Urinary and plasma metabolites include biotransformation products formed via hydroxylation of the tert-butyl group and/or reduction of the carbonyl group of bupropion. Four basic metabolites have been identified. They are the erythro- and threo-amino alcohols of bupropion, the erythro-amino diol of bupropion, and a morpholinol metabolite.

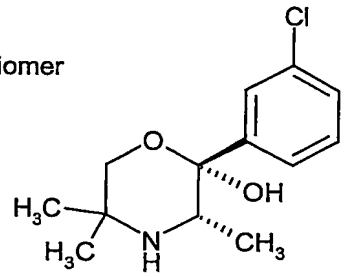
The morpholinol metabolite (+/-)-(2R*,3R*)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol is believed to be formed from hydroxylation of the tert-butyl group of bupropion.



Morpholinol Metabolite of Bupropion

It was discovered that despite the (-) form of the morpholinol metabolite predominating significantly in human plasma samples, it was the (+) enantiomer, (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol in which the optimal monoamine reuptake inhibitory activity resides (WO 99/37305), hereinafter referred to as the compound of formula (I):

(+)-enantiomer



(I)

The compound of formula (I) and its salts and solvates have been disclosed as being of use in the treatment of depression (including major depressive disorder (MDD), bipolar depression (type I and II), major (unipolar) depression and depression with atypical features (eg. lethargy, over-eating/obesity, hypersomnia)), attention deficit hyperactivity disorder (ADHD), obesity, migraine, pain (including neuropathic pain, eg. diabetic neuropathy, sciatica, non-specific lower back pain, multiple sclerosis pain, fibromyalgia, HIV-related neuropathy, neuralgia such as as post-herpetic neuralgia and trigeminal neuralgia and pain resulting from physical trauma, amputation, cancer, toxins or chronic inflammatory conditions), sexual dysfunction (including inhibited sexual desire (low libido), inhibited sexual arousal or excitement, orgasm dysfunction, inhibited female orgasm, inhibited male orgasm, hypoactive sexual desire disorder (HSDD), female sexual desire disorder (FSDD) and sexual dysfunction side-effects induced by treatment with antidepressants of the SSRI-class), Parkinson's disease (including relief from the symptoms of Parkinson's disease which include, but are not limited to, locomotor deficits and/or motor disability, including slowly increasing disability in purposeful movement, tremors, bradykinesia, hyperkinesia (moderate and severe), akinesia, rigidity, disturbance of balance and co-ordination, and a disturbance of posture), Alzheimer's disease, or addiction to cocaine or nicotine-containing (especially tobacco) products (WO 99/37305 and US2003-0064988; both Glaxo Group Limited).

US2003-0032643 (Glaxo Group Limited) discloses the use of the compound of formula (I) and its salts and solvates in the treatment of seasonal affective disorder, chronic fatigue, narcolepsy and cognitive impairment.

US2003-0083330 (Glaxo Group Limited) discloses the use of the compound of formula (I) and its salts and solvates in the treatment of addiction to alcohol.

WO 00/51546 and WO 01/62257 (both Separacor Inc) disclose the use of a bupropion metabolite in the treatment of a disorder that is ameliorated by the inhibition of neuronal monoamine reuptake, sexual dysfunction (including erectile

dysfunction), an affective disorder (including depression, anxiety disorders, attention deficit hyperactivity disorder, bipolar and manic conditions, sexual dysfunction, psycho-sexual dysfunction, bulimia, obesity or weight gain, narcolepsy, chronic fatigue syndrome, seasonal affective disorder, premenstrual syndrome, and substance addiction or abuse), nicotine addicton, a cerebral function disorder (including senile dementia, Alzheimer's type dementia, memory loss, amnesia/amnestic syndrome, epilepsy, disturbances or consciousness, coma, lowering of attention, speech disorders, Parkinson's disease, Lennox syndrome, autistic disorder, autism, hyperkinetic syndrome, schizophrenia, cerebral infarction, cerebral bleeding, cerebral auteriosclerosis, cerebral venous thrombosis and head injury), epilepsy, smoking cessation and incontinence.

Summary of the Invention

The present invention provides the use of (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or a salt or solvate thereof or pharmaceutical compositions thereof in the manufacture of a medicament for the treatment of Restless Legs Syndrome (RLS).

A further aspect of the invention provides a method of treating Restless Legs Syndrome (RLS) in a mammal (human or animal subject) comprising the administration to said subject of an effective amount of (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or a salt or solvate thereof or pharmaceutical compositions thereof.

One further aspect of the present invention provides the use of optically or enantiomerically pure (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or a salt or solvate thereof or pharmaceutical compositions thereof in the manufacture of a medicament for the treatment of Restless Legs Syndrome (RLS).

A yet further aspect of the invention provides a method of treating Restless Legs Syndrome (RLS) in a mammal (human or animal subject) comprising the administration to said subject of an effective amount of optically or enantiomerically pure (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or a salt or solvate thereof or pharmaceutical compositions thereof.

Detailed Description of the Invention

It will be appreciated that references herein to "treatment" extend to prophylaxis, prevention of recurrence and suppression or amelioration of symptoms (whether mild, moderate or severe) as well as the treatment of established conditions.

As used herein, "Restless Legs Syndrome (RLS)" is also known as the Ekbom syndrome and is a sensorimotor disorder with a general-population prevalence of 5–10%. RLS is characterised by stereotypical jerks of the lower limbs, typically during sleep. RLS may also be characterised as an unpleasant twitching, burning or painful sensation, likened by sufferers to 'crawling ants' or 'writhing worms'

in the muscles and bones which usually occurs during the evenings. The sensations usually occur in the calf, sometimes in the thighs and feet and once they have begun, there is an irresistible urge to move the legs to release the feelings and general discomfort. Symptoms are worse or exclusively present at rest, in the evenings and at night, and are relieved by movement. The need to move occurs on average every 20 to 40 seconds and the movements last for about 1 to 5 seconds. For some patients, RLS is mild and causes little inconvenience, in others however, the impact on sleep is considerable, compromising work and social activities (Allen, R. P. and Earley, C. J. (2001) J Clin Neurophysiol;**18**:128–147 and Earley, C. J. (2003) N Engl J Med; **348**:2103–2109). A minority of RLS cases are secondary to a pre-existing condition (pregnancy, renal failure and iron-deficiency anaemia), and resolve with that underlying condition. Minimal criteria for the diagnosis of RLS were published by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 (Walters, A. S. (1995) Mov Disord;**10**:634–642) and updated in 2003 (Allen *et al.* (2003) Sleep Med;**4**:101–119).

The use of the compound of formula (I) or a salt or solvate thereof in the treatment of RLS may result in improvement in the subject's condition as determined by one or more of the following clinical measures, following administration:
PLMI (periodic limb movement index), PLMAI (periodic leg movement with arousal index), PLMW (periodic leg movements during wakefulness), and IRLS (International Restless Leg Syndrome) rating scale, although other measures may also be used as appropriate.

As used herein, "optically or enantiomerically pure" means that the composition contains greater than about 90% of the desired stereoisomer by weight, preferably greater than about 95% of the desired stereoisomer by weight, more preferably greater than about 99% of the desired enantiomer by weight, most preferably greater than 99.5% of the desired enantiomer by weight, said weight percent based upon the total weight of the compound of formula (I).

Preferred for use according to the present invention are pharmaceutically acceptable salts or solvates of the compound of formula (I), particularly those disclosed in WO 99/37305, WO 00/51546 and WO 01/62257. Particularly preferred is (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride.

Preparation

The compound of formula (I) or a salt or solvate thereof may be prepared in isolated form, and preferably in an optically or enantiomerically pure form, in accordance with the procedures set forth in WO 99/37305, US2003-0064988, US2003-0032643 and US2003-0027827 (all of Glaxo Group Limited) or WO 00/51546 and WO 01/62257 (both of Sepracor Inc.) the procedures of which are herein incorporated by reference.

Dosage and Formulation

The compound of formula (I) or a salt or solvate thereof is administered in isolated form, and is preferably administered in an optically or enantiomerically pure form.

The amount of compound of formula (I) or a salt or solvate thereof required to achieve the desired therapeutic effect will, of course depend on a number of factors, for example, the mode of administration and the recipient being treated. In general, the daily dose will be in the range of 0.02 to 5.0 mg/kg. More particular ranges include 0.02 to 2.5 mg/kg, 0.02 to 1.0 mg/kg, 0.1 to 1.5 mg/kg, 0.02 to 0.25 mg/kg, 0.02 to 0.15 mg/kg and 0.02 to 0.07 mg/kg given as a single once a day dose or as single or divided doses throughout the day. Preferably in the treatment of RLS, administration will be at appropriate time(s) of the day so that a peak of plasma concentration of the compound of formula (I) coincides with late evening or bedtime.

The compound of formula (I) or a salt or solvate thereof may be employed in the treatment of Restless Legs Syndrome (RLS) as the compound *per se*, but is preferably presented with one or more pharmaceutically acceptable carriers, diluents or excipients in the form of a pharmaceutical formulation. The carriers, diluents and exipients must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and is preferably formulated with the agent as a unit-dose formulation, for example, a tablet containing 1mg, 2mg, 5mg, 10mg, 20mg, 40mg, 60mg, 80mg, 100mg, 120mg, 150mg and 200mg of the compound of formula (I) or a salt or solvate thereof, more preferably 10-80mg of the compound of formula (I) or a salt or solvate thereof.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a compound of formula (I) or a salt or solvate thereof in a flavoured base, usually sucrose and acacia or tragacanth, and pastilles comprising the agent in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a compound of formula (I) or a salt or solvate thereof, preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the agent with water and rendering the resulting solution sterile and isotonic with the blood.

Formulations suitable for rectal administration are preferably presented as unit-dose suppositories. These may be prepared by admixing a compound of formula (I) with one or more conventional solid carriers, for example, cocoa butter, and then

shaping the resulting mixture.

Formulations suitable for topical application to the skin preferably take the form of an ointment, cream, lotion, paste, gel, spray, transdermal patch, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question.

Biological Data

In vitro Synaptosomal Uptake

In vitro uptake was determined, as reported previously, using synaptosomes prepared from rat caudoputamen (for dopamine uptake) and hypothalamus (for NA and serotonin uptake) using [^{3}H]-dopamine, [^{3}H]-NA and [^{3}H]-serotonin as transport substrates, respectively. *See* Eckhardt, S.B., R.A. Maxwell, and R.M. Ferris, A Structure-Activity Study of the Transport Sites for the Hypothalamic and Striatal Catecholamine Uptake Systems. Similarities and differences. *Molecular Pharmacology*, 21: p. 374-9,1982.

Synaptosomes for use in obtaining in vitro uptake data were prepared from hypothalamus or striatum by gently homogenizing the tissue in a 0.3 M sucrose/25 mM Tris pH 7.4 buffer containing iproniazid phosphate to inhibit monoamine oxidase. The homogenate was centrifuged at 1100 x g at 4°C for 10 min and the supernatant was used for uptake studies. The supernatant (~ 1 mg tissue protein) was incubated with Km concentrations of [^{3}H]-noradrenaline, [^{3}H]-dopamine or [^{3}H]-serotonin at 37°C for 5 minutes in Modified Krebs-Henseleit buffer (118 mM NaCl, 5 mM KCl, 25 mM $NaHCO_3$, 1.2 mM NaH_2PO_4, 1.2 mM $MgSO_4$, 11 mM Dextrose, 2.5 mM $CaCl_2$) in the absence and presence of drug. Under these conditions uptake was linear with respect to both for substrate and tissue (with <5% total substrate transported). Non-specific uptake was defined as uptake at 0°C. [^{3}H]-substrate, which had been transported into synaptosomes, was separated from free [^{3}H]-substrate by filtration over GF/B filters and washing with cold Krebs-Henseleit buffer. The filters were counted for tritum in a liquid scintillation spectrometer.

The data for *in vitro* synaptosomal uptake are presented below as Table 1. The compound of formula (I), inhibited noradrenaline (NA) uptake with an IC_{50} of 1.1 μM. On dopamine (DA) uptake, the compound of formula (I) had an IC_{50} of ~10 μM. The compound of formula (I) showed no inhibition of serotonin uptake at 30 μM.

Table 1

Compound	IC_{50} NA	IC_{50} DA	IC_{50} Serotonin
Formula (I)	1.1 ± 0.07	9.3 ± 0.41	>30

Uptake values are means ± SEM of 3 separate experiments. The IC_{50} values are concentrations (μM) required for 50% inhibition of uptake.

Functional reuptake inhibition on human monoamine transporters

Three separate cell-lines expressing human monoamine transporters for dopamine (hDAT) noradrenaline (hNET) and serotonin (hSERT) were used to measure the functional reuptake inhibiting properties of the compound of formula (I) (as its hydrochloride salt). The following methods were utilised.

Human noradrenaline transporter (hNET): MDCK/hNET (dog kidney) cells (4 x 10^4 cells/well) expressing the human norepinephrine transporter were plated on 96-well format one day before the assay. When the cells were 80% confluent, cell monolayers were washed and preincubated with test compound and/or vehicle in modified Tris-HEPES buffer pH 7.1 at 25°C for 20 minutes, then 25 nM [^{3}H]Norepinephrine was added to make the total volume to 200 μl and the cells were further incubated for 10 minutes. Cells in the well were then rinsed twice, solubilized with 1% SDS lysis buffer and the lysate was counted to determine [^{3}H]Norepinephrine uptake. Non-specific signal was determined in the presence of 10 μM desipramine. Reduction of [^{3}H]Norepinephrine uptake by 50 per cent or more (≥50%) relative to vehicle controls indicated significant inhibitory activity.

Human dopamine transporter (hDAT): CHO-K1/hDAT cells (8 x 10^4 cells/well) expressing the human dopamine transporter (hDAT) were plated on 96-well format one day before the assay. Cells were preincubated with test compound and/or vehicle in modified Tris-HEPES buffer pH 7.1 at 25°C for 20 minutes, then 50 nM [^{3}H]Dopamine was added to make the total volume to 200 μl and further incubated for 10 minutes. Cells in the well were then rinsed twice, solubilized with 1% SDS lysis buffer and the lysate was counted to determine [^{3}H]Dopamine uptake. Non-specific signal was determined in the presence of 10μM nomifensine. Reduction of [^{3}H]Dopamine uptake by 50 per cent or more (≥50%) relative to vehicle controls indicates significant inhibitory activity.

Human serotonin transporter (hSERT): HEK-293/hSERT cells (5 x 10^4 cells/tube) expressing the human serotonin transporter (hSERT) were added into the minitube on 96-tube holder prior to assay. Cells were preincubated with test compound or vehicle in modified Tris-HEPES buffer pH 7.1 at 25°C for 20 minutes, then 65 nM [^{3}H]Serotonin was added to make the total volume to 200 μl and further incubated for 10 minutes. Cells were then washed by filtration through cell harvester four times with PBS buffer containing 0.1% BSA and the GF/B filter was counted to determine [^{3}H]Serotonin uptake. Non-specific signal was determined in the presence of 10μM fluoxetine. Reduction of [^{3}H]Serotonin uptake by 50 percent or more (≥50%) relative to vehicle-control indicates significant inhibitory activity.

Compounds were screened at 10, 1, 0.1, 0.01 and 0.001 μM. These same concentrations were concurrently applied to a separate group of untreated cells and evaluated for possible compound-induced cytotoxicity only if significant inhibition of

uptake was observed. Radioactivity retained on the filters was determined by scintillation counting overnight using a Packard scintillation counter.

The potencies for monoamine reuptake inhibition for the hydrochloride salt of the compound of formula (I) are expressed in Table 2 below as IC_{50} (in μM; mean ± SEM) following three separate experiments, each performed in duplicate (n=3). The compound demonstrated reuptake inhibition at both hDAT (pIC50=6.36) and hNET (pIC50=6.70) but reuptake inhibition was not observed on hSERT (pIC50 < 5) at the highest concentration tested (10μM). No cytotoxicity was observed at any of the concentrations causing reuptake inhibition.

Table 2

Compound	hNET	hDAT	hSERT
Formula (I).HCl	0.20 ± 0.05 (n=3)	0.44 ± 0.01 (n=3)	>10 (n=3)

Claims

1. Use of (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or a salt or solvate thereof or pharmaceutical compositions thereof in the manufacture of a medicament for the treatment of Restless Legs Syndrome.

2. Use according to claim 1 wherein said (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or a salt or solvate thereof is optically or enantiomerically pure.

3. Use according to claim 1 or claim 2 wherein the salt is (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride.

4. Method of treating Restless Legs Syndrome (RLS) in a mammal comprising the administration to said subject of an effective amount of (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or a salt or solvate thereof or pharmaceutical compositions thereof.

5. Method according to claim 4 wherein said (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol or a salt or solvate thereof is optically or enantiomerically pure.

6. Method according to claim 4 or claim 5 wherein the salt is (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride.

ABSTRACT

NOVEL USE

This invention relates to a novel use of (+)-(2S,3S)-2-(3-chlorophenyl)-3,5,5-trimethyl-2-morpholinol hydrochloride.